PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
32390-160392		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17024	21/06/2000	21/06/1999
International Patent Classification (IPC) or national classification and IPC C07D409/12		
Applicant UNIVERSITY OF MARYLAND, BALTIMORE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/01/2001	14.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stellmach, J Telephone No. +49 89 2399 8279

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17024

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, sheets:

1/40-40/40 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 9-15.

because:

☒ the said international application, or the said claims Nos. 9-15 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-23

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-8,16-23
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III ----------

1. Claims 9-15 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(i) PCT**).

2. Under the terms of **Rule 39.1 (iv) PCT**, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a method of treatment of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the alleged effects of the compounds (**Rule 67.1 (iv) PCT**).

SECTION V ----------

1. Prior art

Documents (1) - (6), which were cited in the International Search Report, are considered to represent relevant prior art in this Written Opinion; the numbering will be adhered to in the rest of the procedure.

(1) Eur.J.Med.Chem. **34**, 1093 (1999)
(2) J.Heterocycl.Chem. **21**, 181 (1984)
(3) Farmaco **33**, 963 (1978)
(4) Eur.J.Med.Chem. **19**, 433 (1984)
(5) EP-A-0 079 050
(6) EP-A-0 219 112

2.Novelty

2.1 Document (1) is only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** (see also part VI, certain documents) and since the priority document is not available is not taken into account for the Written Opinion. If the priority date is not valid for the complete claimed subject-matter, document (1) may become relevant prior art in a possible regional / national phase.

2.2 The claimed substituted benzoyl-2-thienyl-hydrazone derivatives with *positive inotropic activity* differ from the structurally closest compounds known from (2) by the **thienyl** group which replaces a **pyridyl** group. The closest compounds with the same

pharmacological activity are disclosed in citation (5) but with regard to several structural changes the claimed compounds are structurally unprecedented (see the introduction of the hydrazone group). Accordingly, the requirements of **Article 33 (2) PCT** appear to be met.

3. Inventive step

3.1 For the assessment of inventive step (**Article 33 (3) PCT**) of the claimed subject-matter, the closest prior art has to be identified (**Rule 5.1 (a) (iii) PCT**). Citation (5) discloses **benzoyl-thienyl** derivatives with the same activity. However, in the cited prior art there is **no incentive** that due to the structural modifications as described above compounds with *positive inotropic activity* would result. Accordingly, in sofar as the problem of the provision of new compounds with *positive inotropic effects* is solved (see the pharmacological data for LASSBio-294 on pages 19 - 31), an inventive step in the sense of **Article 33 (3) PCT** in principle could be recognized.

3.2 However, it is stressed that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity. Expressions in claim 1 like "substituted phenyl" are **speculative** in the sense of **Article 33 (3) PCT**, embracing a great variety of structural possibilities (any organic substituent !) not yet explored by the Applicant, the effect of which cannot be foreseen having regard to the problem underlying the present application. Moreover, such definitions create unnecessary **overlap** and further **selection** situations since such expressions encompass other chemical residues/ heterocycles - including any other moiety being known to illustrate *positive inotropic/ cardiotonic activity*. Furthermore, also the attachment of other biophoric/ pharmacophoric molecules as well as **bioconjugates** are embraced, so that the actual biological activity of e.g. the resulting **hybrid molecules** is unpredictable. Having regard to the specific technical problem underlying the present application it cannot be foreseen, whether such molecules are either an obvious solution or a solution to the problem at all. Finally, such extremely broad generalisations obviously are in contradiction to the basis of (qualitative) **structure-activity-relationships**.

4. Industrial applicability

4.1 No objection re industrial applicability of claims 1 - 8 and 16-23 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties (**Article 33 (4) PCT**).

4.2 For the assessment of the present claims 9 - 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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SECTION VII ----------

1. Since the documents (1) - (6) were not identified in the description and the relevant background art disclosed therein was not briefly discussed, the requirements of **Rule 5.1 (a) (ii) PCT** are not met.
2. The dependent claims are only possible as specific form in conjunction with independent claims of the invention (**Rule 6.4 PCT**).

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SECTION VIII----------

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step (**Article 33 (3) PCT**).

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